EXHIBIT 1

Handbook of Pharmaceutical Excipients

Fourth Edition

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Gelatin

1 Nonproprietary Names

BP: Gelatin
JP: Gelatin
PhEur: Gelatina
USPNF: Gelatin

2 Synonyms

Byco; *Cryogel*; gelatine; *Instagel*; *Solugel*.

3 Chemical Name and CAS Registry Number

Gelatin [9000-70-8]

4 Empirical Formula Molecular Weight

Gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen. Gelatin may also be a mixture of both types.

The protein fractions consist almost entirely of amino acids joined together by amide linkages to form linear polymers, varying in molecular weight from 15 000–250 000.

The JP 2001 also includes a monograph for purified gelatin.

5 Structural Formula

See Section 4.

6 Functional Category

Coating agent; film-former; gelling agent; suspending agent; tablet binder; viscosity-increasing agent.

7 Applications in Pharmaceutical Formulation or Technology

Gelatin is widely used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system,[1] although it is most frequently used to form either hard or soft gelatin capsules.[2–4]

Gelatin capsules are unit-dosage forms that are filled with an active drug and are generally designed for oral administration. Although gelatin is poorly soluble in cold water, a gelatin capsule will swell in gastric fluid to rapidly release its contents.

Hard capsules are manufactured in two pieces by dipping stainless steel pins into a gelatin solution, which is distributed evenly around the pin. The gelatin is then set with a blast of chilled air and dried to remove moisture. The capsule halves are then removed, trimmed and filled before they are joined and closed with a tamper-evident seal. The USPNF 20 permits gelatin that is used to produce hard capsules to contain various coloring agents, antimicrobial preservatives, and sodium lauryl sulfate. Manufacturers may also add a hardening agent, such as sucrose, to hard gelatin capsules. Capsules varying in size from 0.13 to 1.37 mL volume are commercially available.

Soft gelatin capsules are formed from an aqueous gelatin solution that contains a plasticizer such as glycerin or sorbitol. Two soft gelatin strips are formed that run between suitable dies. As the dies meet, capsules are formed by injecting the filling material, followed by the capsule halves being sealed together.

Gelatin is also used for the microencapsulation of drugs, where the active drug is sealed inside a microsized capsule or beadlet, which may then be handled as a powder. The first microencapsulated drugs (beadlets) were fish oils and oily vitamins in gelatin beadlets prepared by an emulsion process.

Low-molecular-weight gelatin has been investigated for its ability to enhance the dissolution of orally ingested drugs.[5] Other uses of gelatin include the preparation of pastes, pastilles, pessaries, and suppositories. In addition, it is used as a tablet binder and coating agent, and as a viscosity-increasing agent for solutions and semisolids.

Therapeutically, gelatin has been used in the preparation of wound dressings[6] and has been used as a plasma substitute, although anaphylactoid reactions have been reported in the latter application.[7] Absorbable gelatin is available as sterile film, ophthalmic film, sterile sponge, sterile compressed sponge, and sterile powder from sponge. Gelatin sponge has hemostatic properties.

Gelatin is also widely used in food products and photographic emulsions.

8 Description

Gelatin occurs as a light-amber to faintly yellow-colored, vitreous, brittle solid. It is practically odorless and tasteless and is available as translucent sheets and granules, or as a powder.

9 Pharmacopeial Specifications

See Table I.

Table I: Pharmacopeial specifications for gelatin.

Test	JP 2001	PhEur 2002	USPNF 20
Identification	+	+	+
Characters	—	+	—
Microbial contamination	—	≤1000/g	+
Residue on ignition	≤2.0%	≤2.0%	≤2.0%
Loss on drying	≤15.0%	≤15.0%	—
Odor and water-insoluble substances	—	—	+
Isoelectric point	+	+	—
Type A	7.0–9.0	6.3–9.2	—
Type B	4.5–5.0	4.7–9.2	—
Acidity or alkalinity	—	+	—
Clarity and color of solution	—	+	—
Sulfur dioxide	—	≤200 ppm	≤0.15%
Sulfite	+	—	—
Arsenic	≤1 ppm	≤1 ppm	≤0.8 ppm
Heavy metals	≤50 ppm	≤50 ppm	≤0.005%
pH	—	3.8–7.6	—
Mercury	≤0.1 ppm	—	—
Peroxides	—	≤100 ppm	—
Phenolic preservatives	—	+	—
Gel strength	—	150–250 g	—

10 Typical Properties

Acidity/alkalinity: for a 1% w/v aqueous solution at 25°C:
pH = 3.8–6.0 (type A)
pH = 5.0–7.4 (type B)
Density:
1.325 g/cm^3 for type A
1.283 g/cm^3 for type B
Isoelectric point:
7–9 for type A
4.7–5.3 for type B
Moisture content: 9–11%.[8] *See also* Figures 1 and 2.

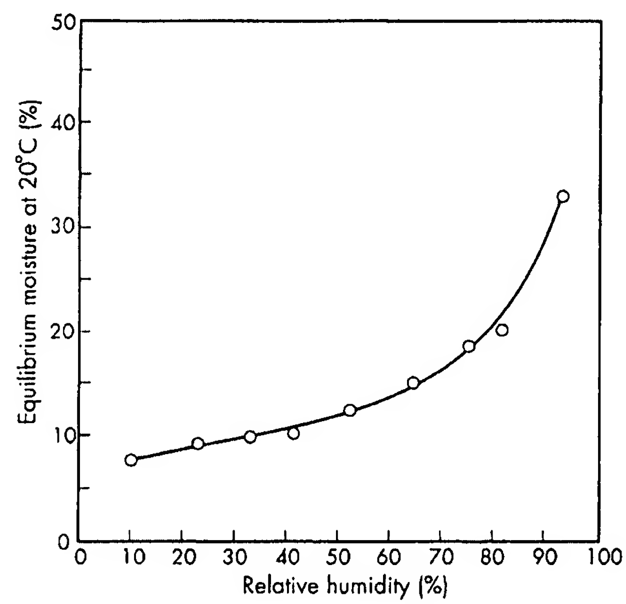

Figure 1: Equilibrium moisture content of gelatin (*Pharmagel A*).

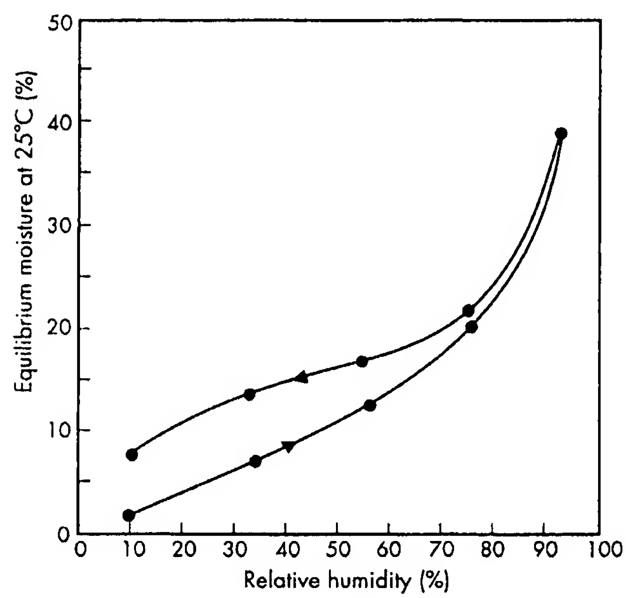

Figure 2: Sorption–desorption isotherm of gelatin.

Solubility: practically insoluble in acetone, chloroform, ethanol (95%), ether, and methanol. Soluble in glycerin, acids, and alkalis, although strong acids or alkalis cause precipitation. In water, gelatin swells and softens, gradually absorbing between 5 and 10 times its own weight of water. Gelatin is soluble in hot water, forming a jelly, or gel, on cooling to 35–40°C. At temperatures >40°C, the system exists as a sol. This gel–sol system is heat-reversible, the melting temperature being slightly higher than the setting point; the melting point can be varied by the addition of glycerin.
Viscosity (dynamic):
4.3–4.7 mPa s (4.3–4.7 cP) for a 6.67% w/v aqueous solution at 60°C
18.5–20.5 mPa s (18.5–20.5 cP) for a 12.5% w/v aqueous solution at 60°C

11 Stability and Storage Conditions

Dry gelatin is stable in air. Aqueous gelatin solutions are also stable for long periods if stored under cool, sterile conditions. At temperatures above about 50°C, aqueous gelatin solutions may undergo slow depolymerization and a reduction in gel strength may occur on resetting. Depolymerization becomes more rapid at temperatures above 65°C, and gel strength may be reduced by half when a solution is heated at 80°C for 1 hour. The rate and extent of depolymerization depends on the molecular weight of the gelatin, with a lower-molecular-weight material decomposing more rapidly.[9]

Gelatin may be sterilized by dry heat.

The bulk material should be stored in an airtight container in a cool, dry place.

12 Incompatibilities

Gelatin is an amphoteric material and will react with both acids and bases. It is also a protein and thus exhibits chemical properties characteristic of such materials; for example, gelatin may be hydrolyzed by most proteolytic systems to yield its amino acid components.

Gelatin will also react with aldehydes and aldehydic sugars, anionic and cationic polymers, electrolytes, metal ions, plasticizers, preservatives, and surfactants. It is precipitated by alcohols, chloroform, ether, mercury salts, and tannic acid. Gels can be liquefied by bacteria unless preserved.

Some of these interactions are exploited to favorably alter the physical properties of gelatin; for example, gelatin is mixed with a plasticizer, such as glycerin, to produce soft gelatin capsules and suppositories; *see* Section 7.

13 Method of Manufacture

Gelatin is extracted from animal tissues rich in collagen such as skin, sinews, and bone. Although it is possible to extract gelatin from these materials using boiling water, it is more practical to first pretreat the animal tissues with either acid or alkali. Gelatin obtained from the acid process is called type A, whereas gelatin obtained from the alkali process is called type B.

In the USA, most type A gelatin is obtained from pig skins. This material is washed in cold water for a few hours to remove extraneous matter and is then digested in dilute mineral acid (HCl, H_2SO_4, H_2SO_3, or H_3PO_4) at pH 1–3 and 15–20°C until maximum swelling has occurred. This process takes approximately 24 hours. The swollen stock is then washed with water to remove excess acid, and the pH is adjusted to pH 3.5–4.0 for the conversion to gelatin by hot-water extraction.

The hydrolytic extraction is carried out in a batch-type operation using successive portions of hot water at progressively higher temperatures until the maximum yield of gelatin is obtained. The gelatin solution is then chilled to form jelled sheets, which are dried in temperature-controlled ovens. The dried gelatin is ground to the desired particle size.

In the alkali process, demineralized bones (ossein) or cattle skins are usually used. The animal tissue is held in a calcium hydroxide (lime) slurry for a period of 1–3 months at 15–20°C. At the end of the liming, the stock is washed with cold water to remove as much of the lime as possible. The stock solution is then neutralized with acid (HCl, H_2SO_4, H_3PO_4) and the gelatin is extracted with water in an identical manner to that in the acid process.

14 Safety

Gelatin is widely used in a variety of pharmaceutical formulations including oral and parenteral products.

In general, when used in oral formulations gelatin may be regarded as a nontoxic and nonirritant material. However, there have been rare reports of gelatin capsules adhering to the esophageal lining, which may cause local irritation.[10] Hypersensitivity reactions, including serious anaphylactoid reactions, have been reported following the use of gelatin in parenteral products.[7]

15 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Gelatin should be handled in a well-ventilated environment.

16 Regulatory Status

Included in the FDA Inactive Ingredients Guide (dental preparations; inhalations; injections; oral capsules, pastilles, solutions, syrups and tablets; topical and vaginal preparations). Included in medicines licensed in the UK.

17 Related Substances

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18 Comments

Various grades of gelatin are commercially available that differ in particle size, molecular weight, and other properties. Grading is usually by gel strength, expressed as 'Bloom strength', which is the weight in grams that, when applied under controlled conditions to a plunger 12.7 mm in diameter, will produce a depression exactly 4 mm deep in a matured gel containing 6.66% w/w of gelatin in water.

Gelatin–acacia complex coacervation has been used in the preparation of microcapsules of vitamin A.[11]

The EINECS number for gelatin is 232-554-6.

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22 Date of Revision

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